15 Aug 03

TO: Patent Examiner Robert M. Joynes

CONCERNING: 09/835,501

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Dr. Joynes,

Concerning the Office Actin Summary (Mailing Date 20 June 03):

I have made the changes in the following:

Claim have been made to properly refer to the First independent Claim (Claim 1) in language suggested.

All reference to Amino Acids other than Acetyl-L-carnitine (and congers) and ornithine (and ornithine HCL) are eliminated.

I have reduce the level of l-ornithine or l-ornithine HCL claimed to a maximum of 1 gram (from the previous 10 grams) as there is no need for this level (unless I were to be increasing GH in whales, all domestic animals are largely below mass that can be affected by the 1 gram level). The just before sleep night time oral ingestion has been restated. The short period of 3-4 hours without nutrient intake needed in this protocol is due to the clearing of the upper gastrointestinal system so that the amino acid uptake receptors for these amino acids are not bombarded by other amino acids that compete for uptake. It does not require a long period, but 3-4 hours are required or competition for uptake will prevent the effect due to a lessening of uptake of this small amount of material. (500 mg of acetyl-l-carnitine and 20-50 milligrams of L-ornithine HCL in humans). Wording has been changed to reflect this fact.

Specific statement of benefit has been changed to reflect specific return

to youthful GH levels rather than general nature of unspecified benefits

Potential overlap/infringement with Gardiner (US 5817329) has been dealt within the next section
(all direct quotes from scientific papers are indented and enclosed in quote marks to separate from other text.

After dealing with potential infringement with Gardiner (US 5817329), I will present evidence that oral intake levels of L-ornithine (or l-ornithineHCL) employed in this application are 2-3 orders of magnitude (powers of 10) below those established to elevate GH release. This is due to the unique synergy between acetyl-l-carnitine and l-ornithine.

Evidence that L-ornithine has different properties than l-ornithine alpha-keto glutarate

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Gardiner (US 5817329) claims synergy of oral intake various amino acids and ornithine a-ketoglutarate. He states in the specifications:

> "The inventor believes that the inclusion of Ornithine alpha-Ketoglutarate prevents muscle breakdown"

In support for this belief and for the inclusion, he cites the reference:

L. Cynober et al, Action of Ornithine Alpha-Ketoglutarate, Ornithine Hydrochloride, and Calcium Alpha-Ketoglutarate on Plasma Amino Acid and Hormonal Patterns in Healthy Subjects, J. Am. Coll. Nutr. 1990; 9(1); 2-12.

This reference specifically draws distinction between the properties of l-ornithine a-ketoglutarate (OKG) and those of l-ornithine (ORN) alone. To quote from this reference:

> "These data provide evidence that the combination of ORN and alpha KG modifies amino acid metabolism in a way which is not observed when they are administered separately. In addition, the OKG-mediated increase in insulin levels probably does not appear to result from a direct action of ORN on

pancreatic secretion."

The unique pharmacological properties of ornithine a-ketogluterate(OKG) that are not shared by l-ornithine have been the source of considerable scientific comment as indicated by the Cynober review article that attributes the combination to involve a synergy between the effects or l-ornithine and that of the a-ketoglutarate component. The a-ketoglutarate component is a precursor to the important anabolic amino acid glutamine which is so important as a growth inducer that it is routinely added to many tissue culture media for that purpose . Thus, this molecule has some unique properties not present in l-ornithine. Further evidence for this important distinction between the effects of l-ornithine(ORN) and that of l-ornithinine apha-ketoglutarate (OKG) is presented below in several scientific papers that elucidate this important distinction.

The importance of the a-ketoglutarate is covered in another paper by Cynober:

Cynober LA: The use of alpha-ketoglutarate salts in clinical nutrition and metabolic care. Curr Opin Clin Nutr Metab Care 1999;2:33-37.
Which states:

> "Theoretically, alpha-ketoglutarate is a precursor of glutamine, a fact that may be of importance given the key regulatory properties of this amino acid. Although the literature suggests that glutamine synthesis accounts only for a marginal part of the disposal of exogenously supplied alpha-ketoglutarate, administered alpha-ketoglutarate has a potent 'sparing' effect on endogenous glutamine pools. When alpha-ketoglutarate is supplied as an ornithine salt, a synergistic effect of the two parts of the molecule increases the synthesis of glutamine or the 'sparing' of endogenous glutamine pools. In addition, alpha-ketoglutarate in combination with ornithine dramatically increases the synthesis of arginine, proline and polyamines, which also play key roles in metabolic adaptation to trauma."

Other scientific papers describe this same distinction between the

pharmacological and physiological properties of L-ornithine (ORN) and l-ornithine a-ketogluterate(OKG) on various systems including the critical insulin secretion system involved in much of maintenance protein synthesis:

Schneid C, Darquy S, Cynober L, Reach G, De Bandt JP: Effects of ornithine alpha-ketoglutarate on insulin secretion in rat pancreatic islets: implication of nitric oxide synthase and glutamine synthetase pathways. Br J Nutr 2003;89:249-257.

> "Ornithine alpha-ketoglutarate (OKG) administration in human subjects elicits insulin secretion...Experiments using alpha-ketoglutarate (alpha-KG) (1 mmol/l) or ornithine (Orn) (2 mmol/l) alone, in concentrations equal to that of OKG, showed that the OKG-induced insulin secretion could not be obtained by either component alone, suggesting that an alpha-KG-Orn interaction is mandatory for the insulin-secreting effect to occur. "

This distinction is also drawn for the maintenance of amino acid levels in normal healthy men. This is particularly important as amino acid levels largely control the rate of protein synthesis in cells.:

Cynober L, Coudray-Lucas C, de Bandt JP, Guechot J, Aussel C, Salvucci M, Giboudeau J: Action of ornithine alpha-ketoglutarate, ornithine hydrochloride, and calcium alpha-ketoglutarate on plasma amino acid and hormonal patterns in healthy subjects. J Am Coll Nutr 1990;9:2-12.

> "These data provide evidence that the combination of ORN and alpha KG modifies amino acid metabolism in a way which is not observed when they are administered separately."

This distinction also hold for trauma and injury and disease status as is common in body builder efforts to increase muscle (all vigorous exercise also involves damage to muscle that must be repaired).

Molimard R, Charpentier C, Lemonnier F: Changes of plasma amino acids in cirrhotics treated with ornithine salts. Ann Nutr Metab 1982;26:25-36.

"The plasma amino acid pattern of cirrhotic patients was determined before and after 24 h of continuous infusions of glucose, ornithine alpha-ketoglutarate (O alpha KG), ornithine chlorhydrate (ORN HCl) and sodium ketoglutarate (alpha CGNa). Before treatment, leucine, isoleucine, valine and glutamine levels were low. Tyrosine and methionine levels were high. (See formula in text) was low. Glucose infusions had no effect. O alpha KG increased levels of leucine, isoleucine, valine, alanine and arginine. Threonine, serine, glycine, aspartic acid, methionine, hemicystine, tyrosine and phenylalanine were significantly lowered. (See formula in text) increased. ORN HCl and alpha CGNa did not induce similar changes."

Thus, L-ornithine alpha-ketoglatarate is not only a different compound than L-ornithine or L-ornithine HCL, but it has different additional pharmacological properties from L-ornithine or L-ornithine HCl

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Evidence that claimed levels of l-ornithine (or ornithine HCL) will not by themselves cause GH release

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Intravenous injection of large amounts of particular amino acids like arginine, lysine, or ornithine can stimulate GH release (basis for the Arginine provocative test for GH competence). Unlike the large intravenous amount of amino acids like arginine (0.5 grams/kilogram of weight in humans, thus some 35 grams intravenously infused to a 70 kg human) that are used to experimentally test whether a human individual can release GH, oral intake of even huge (multigram levels) amounts of single or multiple amino acids including l-ornithine do not have this effect and are limited by stomach upset caused by such large amino acid intake. Oral as opposed to parental (tube delivered to lower gastrointestinal system so get huge bolus rather than the oral route with more diffuse bolus) techniques of elevating GH by oral intake of amino acids have proved to be of no success. Scientific papers listed below show this to be impossible for oral intakes of l-ornithine in the multigram range.

Chromiak JA, Antonio J: Use of amino acids as growth hormone-releasing agents by athletes. Nutrition 2002;18:657-661.

> "Specific amino acids, such as arginine, lysine and ornithine, can stimulate growth hormone (GH) release when infused intravenously or administered orally. Many individuals consume amino acids before strength training workouts, believing this practice accentuates the exercise-induced GH release, thereby promoting greater gains in muscle mass and strength. The GH response to amino acid administration has a high degree of interindividual variability and may be altered by training status, sex, age, and diet. Although parenteral administration consistently leads to increased circulating GH concentration, oral doses that are great enough to induce significant GH release are likely to cause stomach discomfort and diarrhea. During exercise, intensity is a major determinant of GH release. Although one study showed that arginine infusion can heighten the GH response to exercise, no studies found that pre-exercise oral amino acid supplementation augments GH release. Further, no appropriately conducted scientific studies found that oral supplementation with amino acids, which are capable of inducing GH release, before strength training increases muscle mass and strength to a greater extent than strength training alone. "

Even oral intakes of mixtures of 2 grams each of L-arginine, L-ornithine, and L-lysine do not stimulate GH release in humans.
Fogelholm GM, Naveri HK, Kiilavuori KT, Harkonen MH: Low-dose amino acid supplementation: no effects on serum human growth hormone and insulin in male weightlifters. Int J Sport Nutr 1993;3:290-297.

> "Using a double-blind, crossover protocol, we studied the possible effects of a 4-day combined L-arginine, L-ornithine, and L-lysine supplementation (each 2 g/day, divided into two daily doses) on 24-hr level of serum human growth hormone (hGH) and insulin in 11 competitive weightlifters, ages 19 to 35 yrs. Three similar daily hGH peaks, seemingly preceded by a decrease in serum insulin concentration, were found during both amino acid and placebo supplementation. Supplementation did not affect the physiological variation of serum hGH

concentration (treatment and treatment x time interaction: p = 0.43-0.55). Analogously, serum insulin levels were not higher after amino acid supplementation. Therefore the ergogenic value of low-dose oral amino acid supplementation in increasing hGH or insulin secretion seems questionable. "

This absence of effect or L-ornithine (or mixtures of other amino acids above 1 gram in value do not stimulate GH release even after a 8 hour fast Lambert MI, Hefer JA, Millar RP, Macfarlane PW: Failure of commercial oral amino acid supplements to increase serum growth hormone concentrations in male body-builders. Int J Sport Nutr 1993;3:298-305.

"Amino acids are commonly ingested as ergogenic acids in the belief that they enhance protein synthesis and stimulate growth hormone release. The aim of this study was to determine the acute effect that amino acid supplements have on serum growth hormone (GH) concentration. Seven male body-builders reported to the laboratory on four occasions after an 8-hr fast and ingested, in random order, either a placebo, a 2.4-g arginine/lysine supplement, a 1.85-g ornithine/tyrosine supplement, or a 20-g BovrilR drink. Blood was collected before each treatment and again every 30 minutes for 3 hours for the measurement of serum GH concentration. On a separate occasion, subjects had an intravenous infusion of 0.5 microgram GH-releasing hormone.kg-1 body weight to confirm that GH secretory response was normal. The main finding was that serum GH concentrations were not altered consistently in healthy young males following the ingestion of the amino acid supplements in the quantities recommended by the manufacturers. "

These data must be view in the context of the specific synergy claimed by this patent application, namely that for any weight humans, 500 mg of acetyl-l-carnitine and 20-50 milligrams of L-ornithine act in a specific synergy to trigger (only) night time GH release providing ingestion is preceded by a 3 hour period of no intake of nutrients (that may well block or compete for specific uptake receptors for these minute levels of l-ornithine in the upper gastrointestinal system). This involves not only a different compound (L-ornithine or L-ornithine HCL) with a significantly different pharmacology and physiology than the Gardiner (US 5817329)

choice of ornithine alpha-ketoglutrate as demonstrated in above references, but also a specific synergy taking place only at night time period that involves a uniquely different mechanism. Oral intake of l-ornithine alone has no GH releasing properties until multigram levels are reached, and is usually so nauseating that it cannot be sustained, despite the fact that intravenous ingestion of ornithine at high (0.5 grams/Kilogram of body weight) levels will trigger GH release as will similar parental intake levels (tube delivered bolus to stomach or lower gastrointestinal system).

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